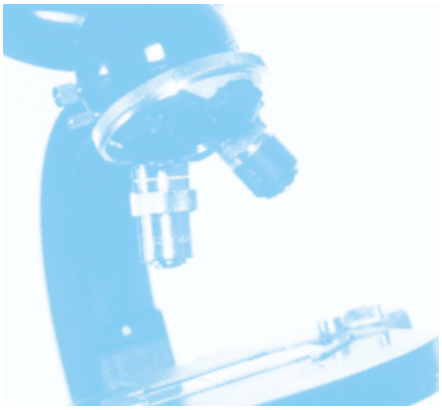

Toolbox

Ectopic pregnancy

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Ectopic pregnancy (figure 1) causes major maternal morbidity and mortality with pregnancy loss, and its incidence is increasing worldwide.[1-3] In northern Europe between 1976 and 1993, the incidence increased from 11.2 to 18.8 per 1,000 pregnancies,[2] and in 1989 the number of admissions to US hospitals for ectopic pregnancy increased from 17,800 in 1970 to 88,400.[4] These changes were greatest in women older than 35 years.[2,4] In the United Kingdom, around 11,000 cases of ectopic pregnancy occur per year (incidence, 11.5/1,000 pregnancies), with 4 deaths (a rate of 0.4/1,000 ectopic pregnancies).[1]

METHODS

We review the incidence, causes, diagnosis, and management of ectopic pregnancy. The evidence presented is from a combination of selected published articles identified from MEDLINE and a reflection of clinical practice at our institution (St James's University Hospital, Leeds, England). For the MEDLINE search, we used the term "ectopic pregnancy" combined with terms such as "incidence," "risk factors," "methotrexate," "salpingectomy," "salpingostomy," and the like.

RISK FACTORS

Although a proportion of women with ectopic pregnancy have no identifiable causal factors, the risk is increased by several factors: previous ectopic pregnancy,[5] tubal damage from infection or surgery,[6] a history of infertility,[6] therapy for in vitro fertilization,[7] increased age,[2,4] and smoking.[8]

A history of pelvic inflammatory disease is particularly important[6,9] and has been implicated in the increased incidence of ectopic pregnancy.[9,10] The risk of an ectopic pregnancy is increased 7-fold after an episode of acute salpingitis.[9] This is particularly true if the causal agent is *Chlamydia trachomatis*, which is the main cause of pelvic inflammatory disease in the United Kingdom.[11] Comprehensive programs to prevent the transmission of chlamydia decrease not only the incidence of *C trachomatis* infections but also the rate of ectopic pregnancies.[12,13]

Previous female sterilization and current use of an intrauterine contraceptive device are risk factors only when patients with ectopic pregnancy are compared with pregnant controls but not with nonpregnant women.[14,15] This is because the overall risk of pregnancy in these situations is low, but if pregnancy does occur, an ectopic pregnancy is more likely.

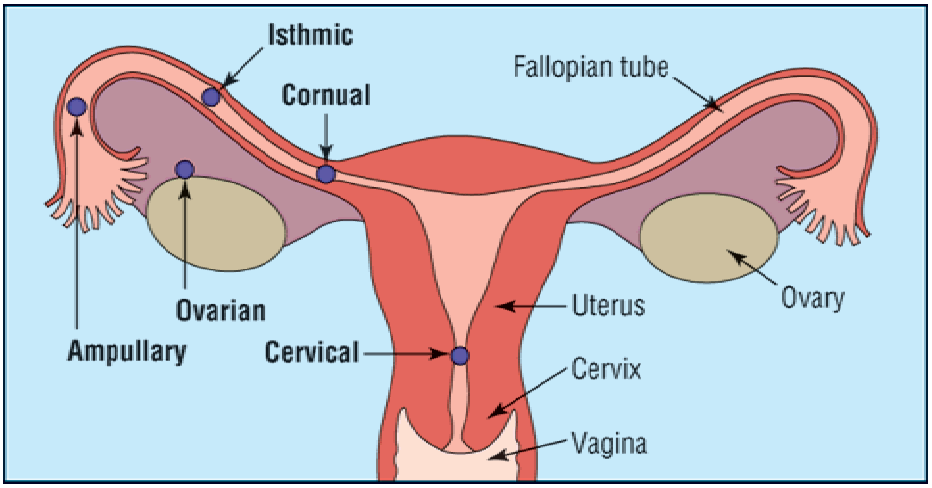

Figure 1 Sites of ectopic pregnancies

Summary points

- The incidence of ectopic pregnancy is increasing, mainly due to the increased incidence of pelvic inflammatory disease caused by *Chlamydia trachomatis*
- Ectopic pregnancy must be excluded in a sexually active woman with a positive pregnancy test, abdominal pain, and vaginal bleeding
- Early ultrasonography should be available in subsequent pregnancies for women who have had an ectopic pregnancy
- Diagnosis cannot be made clinically
- Treatment should be tailored to individual needs; in selected women, medical management can be as effective as laparoscopic salpingostomy
- Conservative surgery results in slightly higher rates of intrauterine pregnancy and a higher incidence of recurrent ectopic pregnancies

The risk of ectopic pregnancy after sterilization is only 7.3 per 1,000 within 10 years.[14]

The incidence of ectopic pregnancy after assisted reproductive techniques is 4%,[7] which is 2 to 3 times greater than the background incidence. The main risk factor in this group is tubal infertility. The incidence of heterotopic pregnancy—an ectopic pregnancy together with an intrauterine pregnancy—is also increased after assisted reproductive techniques.

PRESENTATION

Ectopic pregnancies usually present after a woman has been amenorrheic for 7 (SD 2) weeks. The diagnosis can be difficult unless the condition is suspected, and the condition can be confused with miscarriage, an ovarian accident, or pelvic inflammatory disease (see box). The abdominal pain is usually lateral. However, because as much as 9% of women report no pain and 36% lack adnexal tenderness, the history and physical examination alone do not reliably diagnose or exclude ectopic pregnancy. The presence of known risk

factors can increase suspicion, but any sexually active woman presenting with abdominal pain and vaginal bleeding after an interval of amenorrhea has an ectopic pregnancy until proved otherwise. Women who present in a collapsed state usually have had prodromal symptoms that have been overlooked. Tubal rupture is rarely sudden because it is due to invasion by the trophoblast (figure 2). Therefore, if ectopic pregnancy is at all possible, hospital referral for investigation is mandatory.

HOSPITAL DIAGNOSIS

Referral should preferably be to a consultant or center dedicated to managing problems early in pregnancy because this allows ease of investigation and continuity of outpatient care. The initial investigations are a sensitive pregnancy test and ultrasonography. The presence of an intrauterine pregnancy generally excludes ectopic pregnancy, although other ultrasonographic findings have to be considered, especially if symptoms are atypical, severe, or persistent. The use of quantitative measurement of serum concentrations of β human chorionic gonadotropin (hCG), together with transvaginal ultrasonography, has improved the diagnosis.[16] Controversy exists, however, about the concentration of serum hCG that is diagnostic.[17,18] In the presence of an ectopic mass or fluid in the pouch of Douglas, a cutoff point for a serum concentration of hCG of 1,500 IU/L is recommended, but in the absence of any ultrasonographic signs, the higher concentration of 2,000 IU/L should be the cutoff point before an ectopic pregnancy is diagnosed.[18] Ectopic pregnancies produce lower concentrations of hCG than normal pregnancies, but the change in concentrations provides more information.[19,20] In a normal pregnancy, serum concentrations of hCG double every 2 to 3.5 days in the 4th to 8th week of gestation, reaching a peak around the 8th to 12th week, as calculated from the last menstrual period (figure 3).[20,21] A failure of this increase suggests an ectopic pregnancy, although it is also associated with early pregnancy failure. A 2-day sampling interval has been recommended if paired serum specimens are being tested.[19] The accurate diagnosis of ectopic pregnancy can be lifesaving, reduces the need for invasive investigations, and allows conservative treatment.

Presenting signs with ectopic pregnancy and percentage occurrence of history

Abdominal pain	97%
Vaginal bleeding	79%
Abdominal tenderness	91%
Adnexal tenderness	54%
History of infertility	15%
Use of an intrauterine contraceptive device	14%
Previous ectopic pregnancy	11%

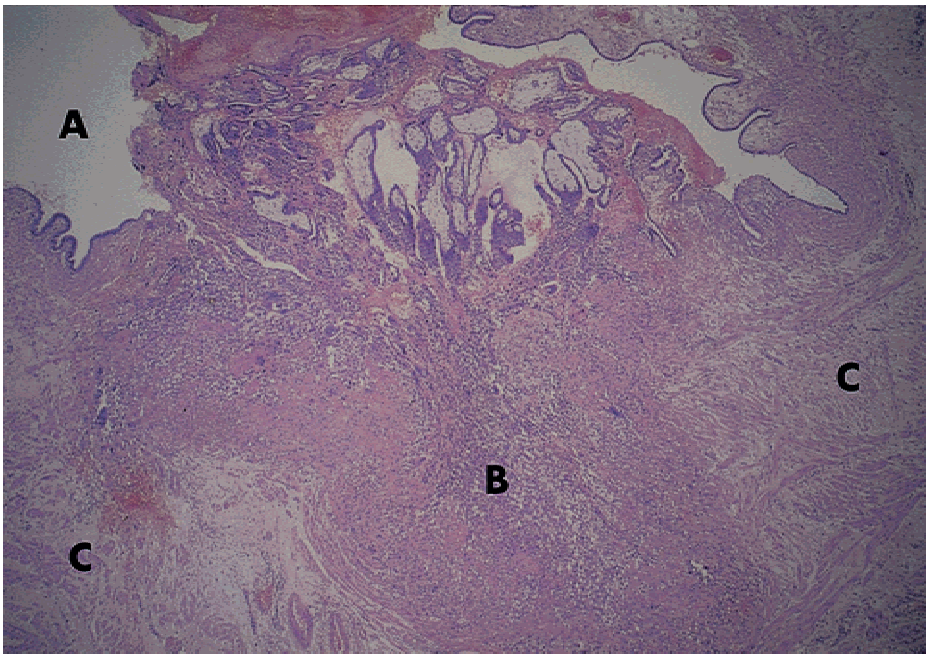

Figure 2 Trophoblast invading wall of fallopian tube, showing tubal lumen (A), trophoblast (B), and tubal wall (C) (original magnification ×25).

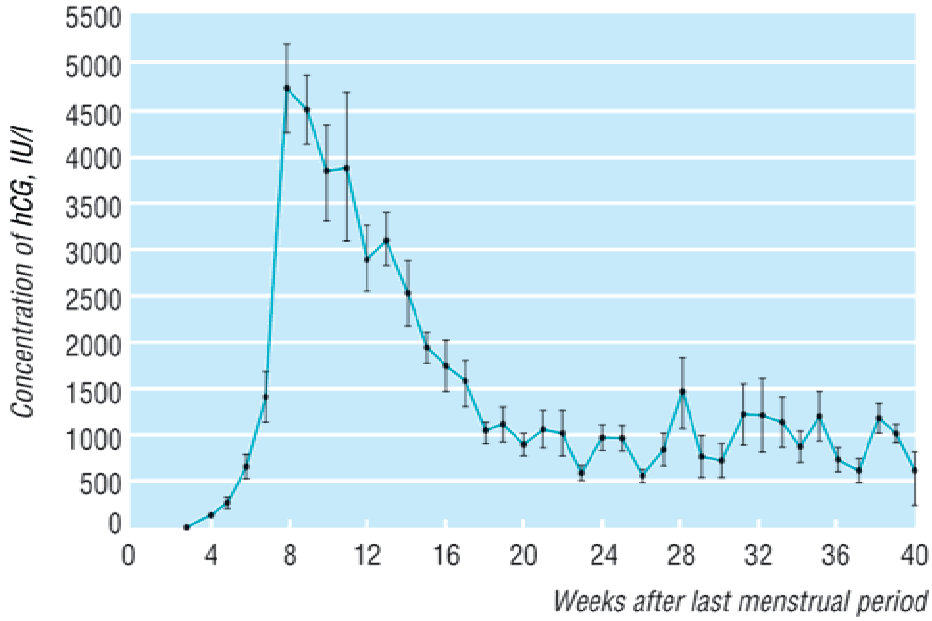

Figure 3 Mean (±SE [bars]) serum concentrations of human chorionic gonadotropin (hCG) levels in normal pregnancy (modified from Braunstein et al[21]).

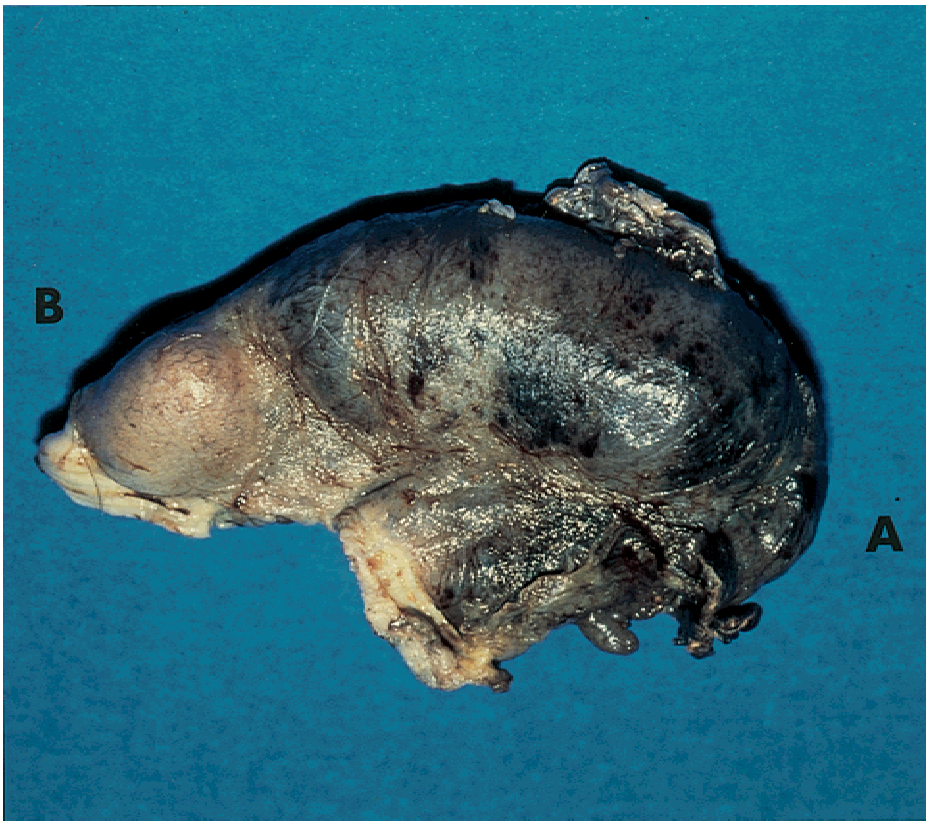

Figure 4 Unruptured tube with ectopic pregnancy, showing the fimbrial end (A), and the cornual end (B).

TREATMENT

Expectant and medical management are possible and should be considered in selected cases, but it is not widely practiced in the United Kingdom. Surgery remains the mainstay of treatment, possibly resulting in many women being overtreated.

Expectant

Some ectopic pregnancies resolve spontaneously, and expectant management is possible in selected women. This is not related to the size of the ectopic pregnancy on an ultrasonogram[22,23] but the initial serum titer of hCG, and the trend in titers is an independent predictor of success.[24] Therefore, serial serum titers of hCG should be monitored in patients who are being managed expectantly. The higher the serum concentration, the more likely expectant management will fail.[22,24] Overall, if the initial serum concentration of hCG is less than 1,000 IU/L, expectant management is successful in as much as 88% of patients.[24]

MEDICAL

Methotrexate, a folic acid antagonist, is used for medical management in patients before rupture who are hemodynamically stable (figure 4).[25] It can be given intramuscularly or injected into the ectopic pregnancy sac, a route that delivers high concentrations locally with smaller systemic distribution. However, rates of successful treatment are lower than with parenterally administered methotrexate, and it requires a laparoscopic or ultrasound-guided needle procedure. Methotrexate in a single dose is more convenient than the variable-dose regimen but may carry a higher risk of persistent ectopic pregnancy.[5] Close follow-up with serial measurements of serum concentrations of hCG is required. A second course of treatment may be necessary, and some patients may require surgical intervention. Methotrexate treatment may produce substantial side effects.

Surgical

Surgical treatments may be radical (salpingectomy) or conservative (usually salpingostomy), and they may be performed by laparoscopy or laparotomy. Salpingectomy is the treatment of choice if the fallopian tube is extensively diseased or damaged because the risk of ectopic pregnancy recurring in that tube is high.

Generally, hospital stay (1.3 days) and convalescence (2.4 weeks) are shorter after laparoscopy than after laparotomy (3.1 days and 4.6 weeks, respectively).[26,27] Both techniques produce similar rates of complications and persistent trophoblast.[27,28] If persistent trophoblast is a risk, follow-up with serial measurements of serum concentrations of hCG is necessary. Because no single postoperative concentration of hCG is predictive, follow-up is necessary until complete resolution.[25] The need for a second laparoscopy should be based on symptoms rather than changes in concentrations of hCG.[26-28] In a randomized controlled trial, methotrexate and laparoscopic salpingostomy were equally effective.[29]

COST OF TREATMENT

The cost of salpingostomy is slightly more than of salpingectomy in the short term.[30] Both treatments are equally effective initially, but additional treatment for persistent ectopic pregnancies is occasionally required after salpingostomy. Although calculating the cost of an acute episode is comparatively simple, calculating the long-term costs of subsequent infertility treatment and treatment of recurrent ectopic pregnancy is more difficult.

The psychological cost is often overlooked because it is not generally viewed in the same way as other pregnancy loss. Women seem to have similar grief reactions as those with miscarriages but have the additional trauma of possibly reduced fertility. Support networks such as the Miscarriage Association are recommended to women after miscarriage, but until recently, no specific support group has been available for women after ectopic pregnancy. A support group in the United States can be found at www.ectopicpregnancy.com.

FERTILITY AFTER TREATMENT

The rates of intrauterine pregnancy after expectant management are comparable to those achieved after medical or surgical management, varying between 80% and 88%,[31,32] and rates for recurrent ectopic pregnancy vary between 4.2% and 5%.

A population-based cohort study reported a pregnancy rate of 66% regardless of whether treatment was surgical or medical.[33] Of those who conceived, 90% achieved an intrauterine pregnancy and 10% had recurrent ectopic pregnancy. The risk factors for recurrent ectopic pregnancy are previous spontaneous miscarriage, tubal damage, and age older than 30 years.[25] After treatment with methotrexate, between 62% and 70% of women had a subsequent intrauterine pregnancy, and around 8% had recurrent ectopic pregnancy.[23,25]

When comparing conservative and radical surgery, the results are conflicting, with pregnancy rates varying from no significant difference[34] to lower rates of both intrauterine pregnancy and recurrent ectopic pregnancy after salpingectomy.[23,35,36]

Irrespective of type of tubal surgery, laparoscopic treatment resulted in a higher rate of intrauterine pregnancy (77% vs 66%)[35] and a lower rate of recurrent ectopic pregnancy (7% vs 17%)[27] compared with laparotomy. A history of infertility is, however, an important factor, with an overall conception rate of 77% for all methods of surgical treatment and a rate of recurrent ectopic pregnancy of around 10%.

Despite tubal preservation in around 90% of patients and patency in 55% to 59%, neither parenteral treatment with methotrexate nor laparoscopic salpingostomy improved subsequent pregnancy performance.[29] Treatment should, therefore, be directed at therapeutic need and the wishes of the patient.

CONCLUSION

Because ectopic pregnancy cannot be diagnosed in the community, all sexually active women with a history of lower abdominal pain and vaginal bleeding should be referred to a hospital early for ultrasonography and, if necessary, measurement of serum concentrations of hCG. Women with a history of ectopic pregnancy should have early ultrasonography to verify a viable intrauterine pregnancy in their subsequent pregnancies. Diagnostic laparoscopy is necessary if the clinical situation cannot be clarified or if the patient's condition deteriorates.

Expectant and medical management of ectopic pregnancy are effective options in selected women as long as adequate facilities for monitoring are available. If surgery is necessary, the laparoscopic route results in a shorter hospital stay, but salpingostomy has no clear advantage over salpingectomy. The decision should, therefore, be made on an individual basis. Methotrexate and laparoscopic salpingostomy are equally successful in treating ectopic pregnancy.[36] Ectopic pregnancy can be prevented by decreasing the incidence of pelvic inflammatory disease and *C trachomatis* infections and improving their treatment.

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